Topiramate-Induced Kidney Stones

In a 2-part study, researchers at the University of Texas retrospectively investigated the prevalence of symptomatic kidney stones and prospectively evaluated the prevalence of asymptomatic kidney stone development in patients treated with topiramate (Topamax).

Methods: Patients (n=150) treated with topiramate were identified in an electronic database of patients from the university hospital. For the retrospective portion of the study, patients were administered a questionnaire by phone that assessed the presence of diagnosed kidney stone disease as well as demographic and illness variables. Patients who reported no symptomatic kidney stone disease were invited to undergo a noncontrast CT scan of the abdomen.

Results: Investigators were able to contact 75 patients (median age, 40 years); all completed the phone questionnaire. Most (n=62) had been receiving topiramate in the range of 188–425 mg/day for a median of 2–4 years to treat a seizure disorder. Of the 75 patients, 8 (11%) reported a history of either spontaneous kidney stone passage, urological treatment for kidney stones, or radiographic evidence of calculi while taking topiramate. Fifteen of the 67 patients with no history of kidney stones agreed to undergo CT scanning. Although asymptomatic, 3 of these patients (20%) had evidence of kidney stone formation. Demographic and illness variables did not differ between patients in whom stones did and did not form. However, there was a tendency toward higher dosages and longer treatment durations in patients with symptomatic stones and toward longer treatment duration in patients with asymptomatic stones.

Discussion: Topiramate inhibits renal carbonic anhydrase, which is believed to predispose treated patients to kidney stone formation. The prevalence of symptomatic stone formation in this study is substantially higher than that reported in short-term clinical studies (≤2%). Furthermore, asymptomatic stones may develop at an increased rate in treated patients. In total, 15% of patients participating in the present study experienced kidney stone development. As the off-label use of topiramate for bipolar disorder and other psychiatric illnesses increases, a large number of patients may experience this complication, many without symptoms.

Maalouf N, Langston J, Van Ness P, Moe O, et al: Nephrolithiasis in topiramate users. Urological Research 2010; doi 10.1007/s00240-010-0347-5. From the University of Texas Southwestern Medical Center, Dallas. Funded by the NIH; and the Pak Center of Mineral Metabolism. The authors did not include disclosure of potential conflicts of interest.
Adjunctive Gabapentin for Schizophrenia

In a small pilot study, adjunctive gabapentin produced additional improvement of schizophrenia symptoms that had been partially responsive to atypical antipsychotics.

Background: Clozapine, currently the recommended drug for refractory schizophrenia, has many drawbacks including high attrition, serious adverse effects, and limited efficacy. Gabapentin is a novel antiepileptic drug, designed as a structural analog of GABA. Its mechanism of action is not fully understood. Like other anticonvulsants being investigated in psychiatric disorders, it has a mild side-effect profile, is safe in overdose, and can be combined safely with other antiepileptics.

Methods: Ten inpatients, aged 27–52 years (9 males), with chronic paranoid schizophrenia were included in the open-label study. All had experienced partial response, defined as a <20% reduction in total Positive and Negative Syndrome Scale (PANSS) score and a score of ≥80 after at least 12 weeks of antipsychotic treatment. Gabapentin was added to olanzapine in 5 patients and to risperidone in 5 patients. Adjunctive gabapentin was started at 100 mg t.i.d. and increased as tolerated to a maximum dosage of 1800 mg/day. All patients received gabapentin for at least 8 weeks.

Results: Total PANSS scores decreased from a mean of 104 at baseline to 78 after 8 weeks of gabapentin treatment (p<0.001). Reductions were comparable in the risperidone and olanzapine groups (30 and 23 points, respectively). A total of 6 patients had PANSS reductions of >50%; 4 taking risperidone (80%) and 2 taking olanzapine (40%). Outcomes did not differ statistically between the 2 antipsychotic drug groups.

Gabapentin was associated with increases in extrapyramidal symptoms, but these became less severe with time. There were no significant changes in Abnormal Involuntary Movement Scale scores after the addition of gabapentin, and scores did not differ between the risperidone and olanzapine groups. Other adverse effects (i.e., sedation, drowsiness, dizziness, and headaches) were mild and transient and did not differ between groups. All patients chose to continue taking gabapentin after the trial.

Gabriel A: Gabapentin adjunctive to risperidone or olanzapine in partially responsive schizophrenia: an open-label pilot study. Neuropsychiatric Disease and Treatment 2010;6:711–717. From the University of Calgary, Alberta, Canada. This study was performed without financial support. The author did not disclose potential conflicts of interest.

Drug Trade Names: clozapine—Clozaril; gabapentin—Neurontin; olanzapine—Zyprexa; risperidone—Risperdal

Bowel Obstruction and Schizophrenia

Constipation is a well-known adverse effect of anticholinergic and antipsychotic medications. It has also been associated with lifestyle factors that may be common in patients with schizophrenia, such as inactivity and low-fiber diets. Severe constipation can lead to bowel obstruction, and related perforations and sepsis can be fatal. Using hospital and prescription registries, the association between antipsychotic medication use and ileus was evaluated in patients with schizophrenia.

Methods: Patients with schizophrenia (n=26,720; mean age, 47 years) treated between 1996 and 2007 were identified from a psychiatric-research database in Denmark. Cases of ileus (n=123) among these patients that were not associated with cancer or other GI illness were identified using linked hospital registries, and antipsychotic use was ascertained from a national pharmacy database.

Results: Risk factors for ileus included increasing age (odds ratio* [OR], 1.03) and female gender (OR, 1.6). Risk was also significantly increased in patients treated with clozapine.
(OR, 1.99), high-potency first generation antipsychotics (OR, 1.81), tricyclic antidepressants (OR, 2.29), anticholinergics (OR, 1.48), and opioids (OR, 2.14). Aripiprazole, amisulpride, and ziprasidone do not appear to be associated with ileus. Of the 123 cases of ileus, 9 were fatal. Five of the 9 patients received multiple antipsychotic medications. Risk of fatal ileus was associated with clozapine treatment (OR, 6.73) and anticholinergic use (OR, 5.88).

Discussion: The authors note that confounding by indication may have affected the results of this study. Clozapine is usually reserved for patients with severe or resistant schizophrenia who as a result of more profound negative symptoms may have more sedentary lifestyles. Most patients treated with clozapine are instructed to take laxatives as well, but this was not evaluated in the study. Similarly, prescription of high-potency, first-generation antipsychotics is often limited to patients with more severe or chronic disease. Ileus is a potentially fatal complication of antipsychotic use, and treated patients (particularly those receiving clozapine or a potent first-generation agent and those with additional risk factors) should be monitored. Prophylactic laxatives may also be helpful.

Nielsen J, Meyer J: Risk factors for ileus in patients with schizophrenia. Schizophrenia Bulletin 2010; doi 10.1093/schbul/sbq137. From Aalborg Psychiatric Hospital, Denmark; and other institutions. Funded by Aalborg Psychiatric Hospital. Both study authors reported commercial relationships with pharmaceutical-industry sources, but no conflicts of interest relevant to the subject of the present study.

Drug Trade Names: amisulpride (not available in the U.S.)—Deniban, Solian, Sulamid; aripiprazole—Abilify; clozapine—Clozaril; ziprasidone—Geodon

*See Reference Guide.

Psychotropics and Violent Behavior

A review of the FDA Adverse Event Reporting System (AERS) shows psychotropic drugs are among agents most frequently associated with reports of violent thoughts and acts.

Methods: Serious adverse event (AE) reports were extracted from the AERS data from 2004 through the third quarter of 2009 in order to identify drugs associated with a disproportionally high rate of violence reports. To be classified as having a disproportional association, drugs were required to have both ≥5 reports and a proportional reporting ratio (PRR) of ≥2. To calculate this ratio, the proportion of AEs that were violence-related was calculated for each drug and for all other drugs combined (after adjustment for the volume of reports). The PRR represents the relative increase in risk.

Results: A total of 484 evaluable drugs produced nearly 800,000 adverse event reports; 1937 of which involved violent thoughts or actions. These included homicide, physical assault or abuse, homicidal ideation, and other violence-related symptoms. Thirty-one drugs met criteria for a dis-proportionate association and accounted for 79% of all violence reports. Drugs that increase the availability of serotonin or dopamine were the most commonly cited, with varenicline as the most frequent. Nearly all of the antidepressants were disproportionately associated with violence (overall PRR, 8.4), as

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<td>Varenicline</td>
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<td>Aripiprazole</td>
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<td>Methylphenidate</td>
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<td>Atomoxetine</td>
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<td>Mirtazapine</td>
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<td>Venlafaxine</td>
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<td>Sertraline</td>
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<tr>
<td>Zolpidem</td>
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<td>Citalopram</td>
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were many ADHD drugs (PRR, 6.9) and several antipsychotics (PRR, 1.9). Among the anticonvulsants, only levetiracetam was identified as associated. Risk was consistently elevated with antidepressants, even when compared with antipsychotics and mood stabilizers, which may be used more often in violence-prone populations. See table for individual PRRs; all are statistically significant at p<0.01.

Discussion: It is important to note that because of the nature of AERS data, the associations cannot be proven as causal. While violence represents a small proportion (<0.5%) of all serious adverse event reports, it appears to be associated with a relatively small group of drugs, most of which are used in psychiatry.

Moore T, Glenmullen J, Furberg C: Prescription drugs associated with reports of violence toward others. *PLoS One* 2010;5 (December):e15337. From the Institute for Safe Medication Practices, Alexandria, Va.; Harvard Medical School, Cambridge Mass.; and Wake Forest University, Winston-Salem, N.C. The study was conducted with no external funding. **The study authors disclosed noncommercial professional relationships with pharmaceutical-industry sources, such as acting as consultants and/or expert witness in litigation involving some of the studied drugs.**

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**Drug Trade Names:**
- alprazolam—*Xanax*  
- aripiprazole—*Abilify*  
- atomoxetine—*Strattera*  
- bupropion—*Wellbutrin, Zyban*  
- citalopram—*Celexa*  
- clonazepam—*Klonopin*  
- desvenlafaxine—*Pristiq*  
- diazepam—*Valium*  
- duloxetine—*Cymbalta*  
- escitalopram—*Lexapro*  
- fluoxetine—*Prozac*  
- fluvoxamine—*Luvox*  
- gabapentin—*Neurontin*  
- levetiracetam—*Keppra*  
- methylphenidate—*Ritalin*  
- mirtazapine—*Remeron*  
- paroxetine—*Paxil*  
- quetiapine—*Seroquel*  
- risperidone—*Risperdal*  
- sertraline—*Zoloft*  
- triazolam—*Halcion*  
- varenicline—*Chantix*  
- venlafaxine—*Effexor*  
- ziprasidone—*Geodon*  
- zolpidem—*Ambien*

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**N-acetylcysteine Use in Psychiatry: Review**

N-acetylcysteine (NAC) may be a useful treatment in psychiatric disorders. Its antioxidant properties may confer nonspecific benefits across a range of mental disorders that involve oxidative stress. It appears to be safe and well tolerated, and it is inexpensive.

NAC is an antioxidant precursor to glutathione, the body’s primary endogenous antioxidant, which maintains the oxidative balance in cells. Oral administration of glutathione does not restore normal levels, but oral NAC does lead to increases in cysteine, the precursor of glutathione, and ultimately increases plasma glutathione. NAC also crosses the blood-brain barrier and raises brain glutathione levels. Glutathione and NAC have been shown to affect glutamatergic and dopaminergic neurotransmission.

NAC has been investigated in a wide range of mental disorders, many of which have limited treatment options or poor outcomes with existing therapies. Most studies have been preliminary in nature. Oxidative stress is a pathway common to addictive disorders; case reports and small, uncontrolled studies suggest NAC may reduce drug use and cravings in dependent adults. Patients with pathological gambling also responded to open-label NAC, and in a subsequent placebo-controlled phase of the study, NAC appeared to prevent relapses.

Oxidative stress has been reported in patients with obsessive-compulsive disorder, an illness that involves similar brain regions to addictive disorders. A single case report showed that the addition of NAC produced marked benefit in a patient partially responsive to fluvoxamine (*Luvox*). Trichotillomania, which shares characteristics with both OCD and addiction, is another candidate for NAC treatment. In a placebo-controlled study in 50 patients, NAC (added to ongoing treatments) reduced symptoms of this disorder. Case reports suggest it may be useful in nail biting and skin picking.

Dysfunction in glutamate metabolism and reduced glutamate in the prefrontal cortex have been reported in populations with schizophrenia. NAC may be beneficial in schizophrenia by targeting both oxidative stress and glutamatergic dysfunction. Adjunctive NAC was investigated in a placebo-controlled trial in 140 patients with refractory schizophrenia. NAC was associated with improvement in negative symptoms, global function, and abnormal movements. Effect sizes
were moderate, and improvements were lost within a month of discontinuing NAC. A qualitative analysis of responses in this study showed that patients who received NAC experienced improvements in insight; self-care; social interaction; motivation; volition; psychomotor stability; and mood stability. A similar trial was carried out in 75 patients with refractory bipolar disorder. Adjunctive NAC was associated with large effect sizes on depression rating instruments and in global disease severity and function. Again, improvements were lost after NAC was stopped.

Dean O, Giorlando F, Berk M: N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *Journal of Psychiatry & Neuroscience* 2011; doi 10.1503/jpn.100057. From the Mental Health Research Institute, Parkville, Victoria, Australia; and other institutions. Funded by the Australian National Health and Medical Research Council; and other sources. One study author disclosed commercial relationships with pharmaceutical-industry sources.

**Newer Antidepressants for Social Phobia**

Second-generation antidepressants appear to be effective in treating social phobia with no consistent differences in efficacy among the drugs.

**Background:** Previous meta-analyses of antidepressant efficacy in social phobia have reached similar conclusions but were based on fewer studies. The present analysis included all identified controlled trials of pharmacotherapy for social phobia, not just those using the predominant assessment instrument, the Liebowitz Social Anxiety Scale (LSAS). The investigators conducted 3 analyses with different outcome measures: the LSAS, Clinical Global Impression Improvement scale (CGI-I), and the standard mean difference. The latter method allows inclusion of any study regardless of the rating scale, because absolute differences in score values are converted into standardized deviations.

**Methods:** A literature search identified 27 randomized placebo-controlled trials comprising more than 8600 adult patients. The trials compared 10 different second-generation antidepressants (i.e., citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, St. John’s wort, venlafaxine) with placebo and in several cases with another active agent. Twenty-one comparisons involved an SSRI, and 8 compared other second-generation antidepressants, including a single trial of St. John’s wort. The studies were heterogeneous, with variable drug doses and treatment durations ranging from 6 to 28 weeks.

**Results:** In CGI or LSAS comparisons, all of the antidepressants, with the exception of mirtazapine and St. John’s wort, were superior to placebo. There were no significant differences between the antidepressants. Overall, second-generation antidepressants as a group were associated with a 62% increase in response rate compared with placebo (with response defined as a CGI rating of “much improved” or better). Paroxetine, venlafaxine, fluvoxamine, sertraline, fluoxetine, and escitalopram were all superior to placebo with no significant between-group differences. Escitalopram appeared to be somewhat less effective than several of the other drugs. In the standardized mean difference comparison, all drugs were similarly effective except for mirtazapine, nefazodone, and St. John’s wort (each investigated in a single trial). No studies of bupropion or duloxetine were identified in the literature.

**Discussion:** This meta-analysis extends the results of previous analyses, which have suggested that second-generation antidepressants improve social phobia with no significant differences in efficacy between the agents.

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**Drug Trade Names:**
- bupropion—Wellbutrin
- citalopram—Celexa
- duloxetine—Cymbalta
- escitalopram—Lexapro
- fluoxetine—Prozac
- fluvoxamine—Luvox
- mirtazapine—Remeron
- nefazodone—Serzone
- paroxetine—Paxil
- sertraline—Zoloft
- venlafaxine—Effexor

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Fracture Risk with Antiepileptics

Antiepileptic drugs, except for valproate, were associated with increased risk of nontraumatic fractures in older patients prescribed the drugs for any indication, according to an epidemiologic study.

Methods: This retrospective cohort study used a health-care database from Canada to identify persons aged ≥50 years with continuous health coverage who had a nontraumatic fracture between 1996 and 2004 and did not take any osteoprotective medication in the previous year. Each case was matched for age, gender, ethnicity, and number of comorbid medical conditions with up to 3 control subjects. Antiepileptic drug exposure categories were nonusers (no agents dispensed within the year prior to the index date), past users (drugs dispensed within the prior year), and current users (drugs dispensed within the prior 4 months). Fracture rates in current users were compared with rates in nonusers.

Results: A total of nearly 16,000 cases were matched with more than 47,000 controls. The most common fracture site was the wrist (52%), followed by the hip (26%) and the vertebra (22%).

Six antiepileptic drugs—carbamazepine; clonazepam; gabapentin; phenobarbital; phenytoin; and valproic acid—were analyzed individually. The number of patients treated with other agents was small, and the groups were combined and evaluated as "other" antiepileptics. All individually evaluated antiepileptics except valproic acid were associated with increased fracture risk. After adjustment for confounding factors, odds ratios* (ORs) for fracture ranged from a low of 1.24 for clonazepam to a high of 1.91 for phenytoin. (See table.) Statistically significant increases in risk were also observed for gabapentin, phenobarbital, carbamazepine, and the "other" category. Presence of comorbid epilepsy, arthritis, substance abuse, depression, schizophrenia, and dementia increased fracture risk. Use of multiple antiepileptic agents also increased risk (OR, 2.97).

Discussion: Antiepileptic drugs have been associated with bone-density reduction, but most previous population-based studies have focused on persons with epilepsy and have not been limited to older individuals. This study is in general agreement with the others in showing that risk is increased with most of the anticonvulsant agents. Prior research on the association of valproic acid with fractures is inconsistent. The association with gabapentin has not previously been reported. It may be explained by the use of this agent to treat pain in patients who may have limited mobility, leading to deconditioning and bone loss. Use of certain psychotropic drugs, which are associated with bone-density loss, may have contributed to the risks in patients with psychiatric illnesses; and antihypertensive drugs, which decrease urinary calcium loss, may have been protective.

Jette N, Lix L, Meige C, Prior H, et al: Association of antiepileptic drugs with nontraumatic fractures. Archives of Neurology 2011:68 (January):107–112. From the University of Calgary, Alberta, Canada; and other institutions. Funded by the Canadian Institutes of Health Research; and Albert Innovates Health Solutions. Several study authors disclosed commercial relationships with pharmaceutical-industry sources.

Drug Trade Names: carbamazepine—Epitol, Tegretol; clonazepam—Klonopin; gabapentin—Neurontin; phenobarbital—Sulfoton; phenytoin—Dilantin; and others; valproic acid—Depakene, Depakote

*See Reference Guide.
Serotonin Reuptake Inhibitors and GI Bleeding: Reminder

Upper gastrointestinal bleeding is a real although small risk with serotonin reuptake inhibitor (SRI) antidepressants, according to a literature review. These agents should not be absolutely contraindicated in any subgroup of patients, however, caution is necessary in those at greater risk of bleeding.

Many reports, including several large epidemiologic studies, suggest that SRIs, but not other antidepressants, are associated with increased risk of upper GI bleeding. Risk is increased with both SSRIs and nonspecific SRIs such as venlafaxine. In some studies, the risks were limited to specific drugs, but these results should be interpreted cautiously because sample sizes may not have been adequate to identify risks with all SRIs. Increased bleeding risk does not appear to carry over to non-GI body sites. Limited evidence also suggests SRIs do not influence risk of ischemic or hemorrhagic stroke.

Increased incidence of abnormal bleeding has not been shown in all studies. When documented, the risks appear to be low, on the order of 1–5 per 1000 patient-years of SRI treatment in unselected patients. Some, but not all, studies indicate the addition of SRIs may increase bleeding risks associated with NSAIDs, antiplatelet drugs, and anticoagulants. Proton pump inhibitor use with SRIs appears to be protective.

Several mechanisms underlie the relationship of SRIs with abnormal bleeding. SRIs inhibit the entry of serotonin from blood into platelets, thereby inhibiting coagulation. They also directly increase gastric acidity, a mechanism that has received little attention in the literature. Several SRIs inhibit cytochrome P450 metabolism and raise blood levels of NSAIDs and antiplatelet drugs. The risk of bleeding is likely to begin when SRIs reach steady state and last until they are washed out of the body. However, a primary pathology, such as a gastric ulcer, must exist for bleeding to occur.

Clinical Implications: SRI use requires additional caution in patients with acid-peptic or liver disease, those undergoing surgery or dental procedures, and in those taking NSAIDs, anticoagulants, or antiplatelet drugs. Non-SRI antidepressants such as mirtazapine and bupropion may be preferable in patients with elevated risk for bleeding. Proton pump inhibitors may be prescribed concomitantly with SRIs in patients at increased bleeding risk.

Andrade C, Sandarsh S, Chethan K, Nagesh KS: Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. Journal of Clinical Psychiatry 2010;72 (December):1565–1575. From the National Institute of Mental Health and Neurosciences, Bangalore, India. This study was not funded. The study authors reported no competing interests relevant to the study.

Drug Trade Names: bupropion—Wellbutrin, Zyban; mirtazapine—Remeron; venlafaxine—Effexor

Multi-Drug Maintenance for Depression in Old Age

Adding a cholinesterase inhibitor to maintenance antidepressant therapy did not prevent depression relapse or improve cognitive outcomes in cognitively intact older adults. In those with mild cognitive impairment, the combination prevented progression to dementia but increased the rate of recurrent depression.

Methods: Study subjects were community-dwelling adults, aged ≥65 years, with unipolar, nonpsychotic major depressive disorder and mild or no cognitive impairment. All patients were treated initially with escitalopram. Those whose depressive symptoms did not respond were switched to duloxetine; and aripiprazole was given as augmentation therapy if necessary. Of 220 patients treated, 158 had a full response, defined as a Hamilton Rating Scale for Depression (HAM-D) score ≤10 for 3 consecutive weeks. Of this group, 130 continued maintenance antidepressant treatment and were randomly assigned to receive added 5–10 mg/day donepezil or...
placebo. Three primary outcomes were assessed at 12 and 24 months: neuropsychological function, using 17 multi-domain tests; cognitive impairment, using the Performance Assessment of Self-care Skills (PASS); and recurrent major depression, using Structured Clinical Interview for DSM-IV or the HAM-D and confirmation by a psychiatrist not involved in the study.

**Results:** After 1 year, patients who received donepezil showed a small benefit in overall global neuropsychological function. It was not sustained at year 2. Of the 5 cognitive domains studied, 2—memory and executive function—remained significantly improved at 2 years with donepezil. Donepezil had marginal effects on cognitive activities of daily living. Depression recurred in 35% of the donepezil group and 19% of the placebo group (p=0.05).

When the 57 patients with mild baseline cognitive impairment were analyzed separately, donepezil was associated with a lower rate of conversion to dementia: 10% vs 33% with placebo (p=0.05). Rates of recurrent depression in this group were 44% with donepezil and 12% with placebo (p=0.03). Two of these patients experienced new-onset mania, and 1 attempted suicide. The 73 patients with initially normal cognition showed no cognitive benefit with donepezil and no increase in recurrent depression.

**Discussion:** In the elderly, cognitive impairment is a core feature of depression that does not resolve fully even when other depressive symptoms do. Depression is believed to be a risk factor or a prodrome for dementia, and executive dysfunction may increase risk of depression recurrence. Although these findings suggest some promise for cholinesterase inhibitors in late-life depression, these drugs may also induce symptoms of depression. The present study suggests that the positive effects of cholinesterase inhibitors in mild cognitive impairment—modest and transient cognitive and functional improvement and postponement of conversion to dementia—must be weighed against the risk of inducing depression and the possible appearance of mania and suicidal behavior.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.


**Drug Trade Names:** aripiprazole—Abilify; donepezil—Aricept; duloxetine—Cymbalta; escitalopram—Lexapro

**Reference Guide**

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.